IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Liversidge et al.
Title:	STERILE FILTERED NANOPARTICULATE FORMULATIONS OF BUDESONIDE AND BECLOMETHASONE HAVING TYLOXAPOL AS A SURFACE STABILIZER
Appl. No.:	10/035,324
Filing Date:	01/04/2002
Examiner:	Haghighatian, Mina
Art Unit:	1616
Confirmation Number:	2223

DECLARATION UNDER 37 C.F.R. §1.132

The undersigned, Gary Liversidge, hereby declares as follows:

I. Background of Gary Liversidge

1. I received my PhD in 1981 from the University of Nottingham, England in Pharmaceutical Chemistry. I have been working in the field of nanoparticulate drug technology since 1987, when I joined Eastman Pharmaceuticals.

2. Through a series of business transactions, Eastman Pharmaceuticals became Sterling Winthrop Pharmaceuticals Research Division, which became known as NanoSystems. The business is currently known as the Elan Drug Technologies (EDT) business division of Elan Corp., PLC. Intellectual property developed at EDT is owned by Elan Pharma International Ltd., (an affiliate of Elan Corp., PLC), which is the assignee of the above-referenced patent application.

3. For clarity of the record an in the spirit of full disclosure, the first named inventor of the instant application is Elaine Liversidge, my wife, who has also worked at the various EDT predecessor companies over the years. She is currently a Sr. Director of the Exploratory Early Stage Division (ESD) of EDT.

4. I currently hold the position of Vice-President and Chief Technology Officer of EDT with offices at 3500 Horizon Drive, King of Prussia, PA 19406.

II. Decision on Appeal No. 2010-005029

5. I have received and thoroughly reviewed the Decision on Appeal dated September 28, 2010 and the cited reference, U.S. Patent Application Publication No. 2007/0117862 by Desai et al. ("Desai").

6. I understand that the Board concluded that there was no "persuasive reason as to why the skilled worker would have restricted Desai's teachings to its working examples" (Decision, page 9, 1st full paragraph). I also understand that despite Desai's statement that no conventional surfactant was used (*id.*, page 5, FF5), the Board relied on Desai's alternative embodiments concerning the use of different surfactants (*id.*, page 6, FF9 & FF10).

III. Example 23 of Desai fails to teach any conventional surfactants which can be used as equivalents to the surface stabilizers of the claimed invention

7. FF9 refers to paragraphs [0271], [0272] and [0274]-[0280] of Desai, and FF10 refers to paragraphs [0283]-[0284] of Desai. More specifically, both FF9 and FF10 are excerpts from Example 23, subsection C, entitled "Formation of Nanoparticles by Spontaneous Microemulsion."

8. Example 23 of Desai describes how to form spontaneous emulsions having a droplet size of below 1000 Å in the dispersed phase. *See* paragraph [0254]. The surfactants or co-surfactants are used for spontaneously forming oil-in-water microemulsions without causing

precipitation of the ***dissolved drug molecules***. *See* paragraphs [0271] and [0272] cited by FF9. The solvent, surfactants, and co-surfactants in the Desai composition can be removed and additional ingredients can be added to the microemulsion. *See* paragraphs [0274]-[0280] cited by FF9.

9 Example 23 of Desai further describes that the process of forming a microemulsion can be modified. For example, a polymer can be added to the solvent to form a matrix, or a water soluble polymer can be added to the external aqueous phase of the microemulsion to alter the solid-form property of the microemulsion. *See* paragraphs [0283] and [0284] cited by FF10.

10. It is my opinion that the skilled artisan would have understood that these surfactants or co-surfactants of Desai, which are used to prevent precipitation of ***solubilized*** drugs during formation of ***oil-in-water microemulsions***, function differently from the surface stabilizers of the claimed invention. In contrast to the compositions of Desai, in the claimed invention the surface stabilizers are adsorbed on the surface of the ***solid nanoparticulate active agent particles*** to prevent the ***solid particles*** from agglomeration or aggregation.

11. In my opinion, it is clear that the surfactants or co-surfactants of Desai's microemulsion are different from the surface stabilizers of the claimed invention because optional removal of the surfactants or co-surfactants, as taught by Desai, would have caused the nanoparticulate active agent particles of the claimed invention to agglomerate or aggregate.

12. It is also my opinion that the skilled artisan would have understood that the polymers for forming a matrix or for alteration of solid-form properties are not functional equivalents to the surface stabilizers of the claimed invention because these polymers are optional ingredients in Desai's composition and do not adsorb on the surface of the active agent particles to prevent the particles from agglomeration or aggregation.

IV. Desai fails to teach how to obtain the claimed nanoparticulate active agent composition in the absence of a protein surface stabilizer

13. My opinion presented in Paragraph 9, above; *e.g.*, that the surfactants of Desai function to prevent precipitation of solubilized drug, in contrast to the present invention's use of surfactants to *maintain the solid, particulate, form of a drug*, is supported by the data given in the examples of Desai.

14. Examples 1, 2, 4, 5, 8, 9, 13, 14, 16, 18, 19, and 23 of Desai describe preparation of nanoparticles in the presence of a protein, human serum albumin (HSA).[1] All of the examples refer to *dissolving* the active agent in a solvent, followed by adding the dissolved drug to a solution of HSA. *See* the Table below.

Example	Relevant Text
1	"30 mg paclitaxel is *dissolved* in 3.0 ml methylene chloride. The solution was added to 27.0 ml of human serum abumin solution (10% w/v)." Paragraph [0189] of Desai.
2	"A series of experiments was conducted employing a similar procedure to that described in Example 1, but a surfactant such as Tween 80 (1% to 10) is added to the organic solvent. . . . From these results it can be concluded that the conventional solvent evaporation method utilizing conventional surfactants in combination with a protein such as albumin is not suitable for the formation of submicron drug particles (e.g. Paclitaxel) without a polymeric core, while using a polar solvent (e.g., methylene chloride)." Paragraphs [0191]-[0192] of Desai.
4	"30 mg Taxol is *dissolved* in 0.55 ml chloroform and 0.05 ml ethanol. The solution is added to 29.4 ml of human serum abumin solution (1% w/v), which is presaturated with 1% chloroform." Paragraph [0195] of Desai.
5	"225 mg Taxol is *dissolved* in 2.7 ml chloroform and 0.3 ml ethanol. The solution is added to 97 ml of human serum abumin solution (3% w/v)." Paragraph [0197] of Desai.
8 (there is no example 6 or 7)	30 mg Isoreserpine (a model drug) is *dissolved* in 3.0 ml methylene chloride. The solution is added to 27.0 ml of human serum abumin solution (1% w/v). Paragraph [0199] of Desai.
9	30 mg Isoreserpine is *dissolved* in 2.7 ml methylene chloride and 0.3 ml ethanol. The solution is added to 27.0 ml of human serum abumin solution (1% w/v). Paragraph [0201] of Desai.
13	"30 mg cyclosporine is *dissolved* in 3.0 ml methylene chloride. The solution is then added into 27.0 ml of human serum albumin solution (1% w/v)." Paragraph [0209] of Desai.
14	"30 mg cyclosporine is *dissolved* in 3.0 ml of a suitable oil (sesame oil containing 10% orange oil). The solution is then added into 27.0 ml of human serum albumin solution (1% v/w)." Paragraph [0211] of Desai.
16	"Weigh out 1.0 g of paclitaxel in a glass bottle. Combine $CHCl_3$ and ethyl alcohol in

[1] The working examples of Desai are not consecutively numbered. For instance, examples 6, 7, 11, 24 and 59 are missing. An example 22 appears after example 23, and an example 40 appears after example 58.

Example	Relevant Text
	appropriate proportions in a vial. Mix well. To the paclitaxel, add 13.33 ml of the chloroform/ethyl alcohol mixture. Agitate to ensure all paclitaxel *dissolves* into solution. . To the *dissolved* paclitaxel solution in the glass bottle, add the HSA solution." Paragraphs [0223]-[0224] of Desai.
18	"Taxol was *dissolved* in USP grade soybean oil at a concentration of 2 mg/ml. 3 ml of a USP 51 human serum albumin solution was taken in a cylindrical vessel that could be attached to a sonicating probe. The albumin solution was overlayered with 6.5 ml of soybean oil/Taxol solution." Paragraph [0234] of Desai.
19	"20 mg paclitaxel is *dissolved* in 1.0 ml methylene chloride. The solution is added to 4.0 ml of human serum abumin solution (5% w/v)." Paragraph [0237] of Desai.
23	The procedure described in Example 16 is repeated using an organic solvent to *dissolve* Taxol at a relatively high concentration." Paragraph [0251] of Desai.

15. Example 3, which also refers to dissolving a drug in a solvent, describes data showing that "it is not possible to form nanoparticles while using conventional surfactants, without a polymeric core material, with pharmacologically active agents which are soluble in polar, water immiscible solvents . . ." Paragraph [0193] of Desai. In this example, taxol is dissolved in chloroform and ethanol, and the solution is added to a Tween 80 solution which is presaturated with 1% chloroform. "The resulting dispersion was opaque, and contained large needle-like crystals of the drug. The initial size of the crystals . . . was 0.7-5 micron. Storage of the dispersion for several hours at room temperature led to further increase in crystal size, and ultimately to precipitation." Paragraph [0194] of Desai.

16. Example 10 describes data showing that when the drug is not completely dissolved in a solvent, the resultant composition is not suitable for the invention. In this example, "30 mg Taxol is dispersed in 0.6 ml ethanol. At this concentration (50 mg/ml), the Taxol is not completely soluble and forms a supersaturated dispersion. The dispersion is added to 29.4 ml of human serum abumin solution (1% w/v)." Paragraph [0203] of Desai. The resulting taxol particle size "extremely broad, ranging from about 250 nm to several microns," with "large particles and typical needle shaped crystals of taxol." *Id.* The example concludes that "that the use of solvents such as ethanol that are freely miscible in water in the invention process results in the formation of large particles with very broad particle size distribution and as such cannot be used alone for the invention process. Thus the invention process specifically excludes the use of

water miscible solvents when used alone for the dissolution or dispersion of the drug component. The invention process requires that such solvents, when used, must be mixed with essentially water immiscible solvents to allow production of the invention nanoparticles." Paragraph [0204] of Desai.

17. Examples 12, 17, 20, 21, and first Example 22 (paragraphs [0245]-[0250] of Desai), 31-58 (paragraphs [0309]-[0389] of Desai), 40 (paragraphs [0390]-[0400] of Desai) and 60-66 (paragraphs [0401]-[0430] of Desai) do not discuss methods of making or formulations of nanoparticulate drugs.

18. Example 15 describes preparation of an anti-asthmatic drug by first dissolving the drug in a solvent, followed by dispersing the dissolved drug in an aqueous protein solution to form the emulsion. Paragraph [0217] of Desai.

19. The second Example labeled 22 (paragraphs [0287]-[0290] of Desai), and Examples 25 and 27 describe preparation of nanoparticles using a protein, casein. In the process of these examples, cyclosporin A is dissolved in a solvent (butyl acetate or toluene), mixed with a solution of Triton X-100:n-Butanol, and mixed with a solution of casein. Paragraphs [0287], [0291], and [0296] of Desai.

20. Example 26 describes forming a microemulsion of cyclosporine but fails to describe the formation of any solid nanoparticles of cyclosporine. ("The microemulsion was evaporated to give a clear liquid containing 5 mg/ml of cyclosporine." Paragraph [0294] of Desai.)

21. Example 28 describes "Preparation of Nanoparticles of BHT", or butylated hydroxyl toluene. Paragraph [0297] of Desai. The example indicates that the formulation was prepared according to Example 24, which does not exist in Desai's description.

22. Example 29 describes preparation of nanoparticles of paclitaxel, where paclitaxel was dissolved in butyl acetate, and added to Triton x-100:propylene glycol, which is a surfactant. It is unclear whether the disclosed particle size of 7-9 nm is that of the ***drug particles*** or that of the ***micelles of Triton x-100***. As shown in the appended Exhibit A, when the concentration of the surfactant is higher than the critical micelle concentration (CMC), the surfactant exists in the phase of a micelle. The CMC for Triton x-100 is reported to be 0.3 mM. The concentration of Triton x-100 in the composition of Example 29 is well above the CMC of Triton x-100. Therefore, Triton x-100 is expected to form micelles in the composition of Example 29. Moreover, the z-average diameter of a micelle of Triton x-100 is reported to be 7.5 nm. Accordingly, it is unclear from Example 29 whether the disclosed particle size of 7-9 nm is that the ***drug particles*** or that of the ***micelles of Triton x-100***.

23. Example 30 discusses phase diagrams of various surfactant/co-surfactant nanoemulsions incorporating various forms of butyl acetate. At paragraph [0305] the particle size of the resultant emulsion droplets are reported. Here, it is clear that both the Sudan II dye and BHT (Butylated hydroxytoluene) were dissolved in butyl acetate (i.e., they are not solid particles) and the resultant emulsion droplets had a particle size of 20-50 nm.

24. At paragraph [0306] of Example 30, Desai conducts "control samples," which do not contain the butyl acetate. Sudan III was added to the surfactant/PG and stirred over a 24 hour period. Desai states that the Sudan III dissolved. In contrast, when the experiment was done with BHT, Desai states that "no dissolution of BHT was observed." This paragraph then makes a series of contradictory statements.

25. The first contradictory statement in paragraph [0306] is that the particles sizes before evaporation of the samples (assumed to be both the Sudan III and the BHT control samples) were 20-50 nm. It is my scientific opinion that if no dissolution of BHT was observed, it is illogical to report a particle size.

26. The second contradictory statement is in paragraph [0307] where Desai states that the samples (again assuming that what was meant was both the Sudan III and the BHT control samples) were filtered through a 0.2 micron filter *after* evaporation. It is my scientific opinion that it is not technically possible to filter dry particles (i.e., after evaporation) through a 0.2 micron filter.

27. In my opinion, Desai's working examples, when taken as a whole, fail to teach that a nanoparticulate active agent composition can be obtained by employing conventional surfactants as surface stabilizers adsorbed on the surface of active agent solid particles to maintain the nanoparticulate size of the active agent.

V. Desai would have led the skilled artisan away from using surfactants in preparation of nanoparticles

28. Desai compares preparation of nanoparticles in the presence of protein alone with preparation of nanoparticles in the presence of conventional surfactants. As demonstrated by Example 1, paclitaxel nanoparticles were successfully prepared in the presence of human serum albumin. However, the use of a conventional surfactant, such as Tween 80, either alone or in combination with human serum albumin, resulted in formation of large paclitaxel crystals. See Examples 2 and 3.

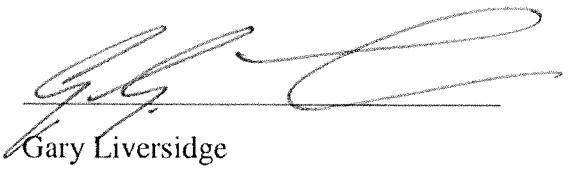
29. It is my opinion that reading Desai in its entirety would lead the skilled artisan to the conclusion that proteins are a *critical* component of Desai's invention. There is no other disclosure in Desai that would convince one of ordinary skill in the art to understand Desai's teachings without being restricted to the working examples.

CONCLUSION

30. Contrary to the Board's conclusion, Example 23 of Desai does not describe an alternative embodiment where conventional surfactants and co-surfactants can serve as a functional equivalents to surface stabilizers of the claimed invention.

31. Contrary to the Board's conclusion, the skilled artisan would have restricted the teachings of Desai to those described by the working examples concerning preparation of nanoparticles using a protein as a stabilizer or preparation of microemulsions of active agents, which are distinguishable from the claimed invention.

32. I declare that the statements made herein of my knowledge are true and all statements on information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therein.



Gary Liversidge

2/25/2011

Date

EXHIBIT A

Surfactant micelle characterization using dynamic light scattering

Introduction

Surfactants belong to a class of molecules with surface active properties. This behavior is due to their amphiphilic structure which contains both a polar or hydrophilic head and a non-polar or hydrophobic tail [1].

Surfactants are normally classified according to the head group type [2]:

- Ionic (anionic and cationic)
- Non-ionics
- Amphoterics (zwitterionics)

Adsorption of ionic surfactants onto a surface generates charge. Cationic surfactants will lead to a positively charged surface and, anionic surfactants will give a negatively charged surface.

Non-ionic surfactant molecules have no charge in aqueous media but normally consist of a highly polar region such as polyoxyethylene groups. Amphoteric surfactants develop a negative or positive charge depending on the pH of the solution.

At low concentrations, surfactant molecules are unassociated monomers. As the concentration of surfactant is increased, the attractive and repulsive forces between the molecules cause self-aggregation to occur resulting in the formation of monolayers or micelles (Figure 1). The concentration at which these micelles form is called the critical micelle concentration (cmc). The characteristics of micelles can be controlled by small changes in the chemical structure of the surfactant molecules or by varying the conditions of the disperse phase. Changes in the pH, ionic strength and temperature are all known to influence the size and shape of surfactant micelles. For some cases, the micelle size can be affected by the concentration of surfactant.

Surfactant micelles have been studied with various techniques [3-5]. This application note discusses the use of light scattering techniques in various aspects of surfactant characterization.

Dynamic light scattering (DLS) is a technique used for particle sizing of samples, typically in the sub-micron range. The technique measures the time-dependent fluctuations in the intensity of scattered light from a suspension of particles undergoing random, Brownian motion. Analysis of these intensity fluctuations allows for the determination of the diffusion coefficients, which in turn yield the particle size through the Stokes-Einstein equation.

Conventional DLS instruments use a detection angle of 90° and this optical configuration may not be sensitive enough for the successful measurement of surfactant micelles.

The Zetasizer Nano range of instruments incorporates non-invasive back scatter (NIBS) optics [6-8]. The scattered light is detected at an angle of 173° and this novel optics arrangement maximizes the detection of scattered light while maintaining signal quality. This provides exceptional sensitivity that is required for measuring the size of nanoparticles, such as surfactant micelles, at low concentrations.

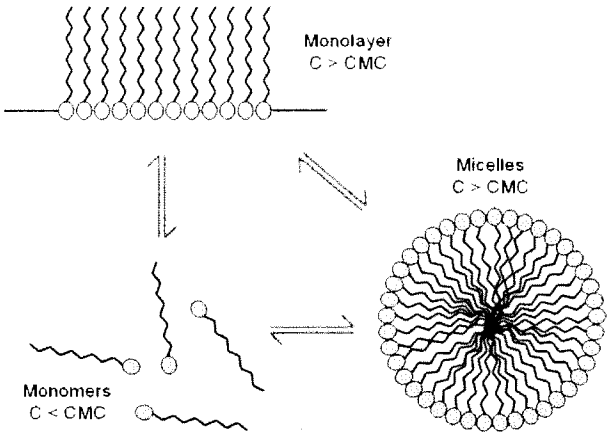


Figure 1: The surfactant can exist as different phases depending upon the concentration of the sample

Experimental

All measurements reported in this application note were performed on a Zetasizer Nano S at 25°C. The Nano S contains a 4mW He-Ne laser operating at a wavelength of 633nm and an avalanche photodiode (APD) detector.

Results

Size Characterization of Surfactant Micelles

Particle size measurements were made of various surfactant micelles on a Zetasizer Nano S. Table 1 summarizes the z-average diameters in nanometers and the polydispersity index values for each sample. The micelles were prepared at twice the critical micelle concentration of the surfactant. The z-average diameter is the mean hydrodynamic diameter and the polydispersity index is an estimate of the width of the distribution. Both of these parameters are calculated according to the International Standard on dynamic light scattering, ISO13321 [9].

The sensitivity of the NIBS optics incorporated in the Zetasizer Nano series enables easy size determination of surfactant micelles to be made without the need of a high-powered laser.

Determination of the Critical Micelle Concentration

The critical micelle concentration of surfactants has been reported using various techniques such as conductivity, surface tension and fluorescence measurements [3-5].

Dynamic light scattering is a technique well suited for the determination of the cmc. In the results summarized here, measurements were made of different concentrations of triton X-100 prepared in deionised water. Below the cmc, the intensity of scattered light detected from each concentration was similar to that obtained from water. In addition, the autocorrelation functions obtained showed very poor signal to noise ratios i.e. very low intercepts and no size distribution information could be obtained from this data. However, once the cmc was reached, the intensity of scattered light increases due to the presence of micelles and the intercepts obtained in the correlation functions are much higher. Figure 2 shows the correlation functions obtained for the 0.05mM (below the cmc) and 0.6mM (above the cmc) concentrations of triton X-100 respectively.

Figure 3 is a plot of the intensity of scattered light (in kilo counts per second) and micelle size (in nanometers) as a function of triton X-100 concentration (mM). The intensity data shows that the scattering detected for triton X-100 concentrations below the cmc are similar to that of deionised water. When the cmc is reached, the scattering intensity shows a linear increase with concentration. The intersection between the 2 lines at 0.25mM concentration corresponds to the cmc of triton X-100 which is in good agreement with literature values [10].

Table 1: z-average diameters (in nanometers) and polydispersity index values obtained for various surfactant micelles on a Zetasizer Nano S. All samples were measured at twice the critical micelle concentration of the surfactant.

Surfactant	Critical Micelle Concentration (mM)	z-Average Diameter (nm)	Polydispersity Index
Triton XL-80N	0.195	7.0	0.062
Triton X-100	0.3	7.5	0.055
Tween 20	0.059	8.5	0.211
Tween 80	0.012	10.7	0.167
Nonidet P40	0.25	15.4	0.207

Determination of Micelle Aggregation Number

The aggregation number of a micelle is defined as the number of surfactant molecules per micelle and is often dependent upon the conditions of the disperse phase [11]. The aggregation number of a micelle can be determined if the molecular weights of the micelle and the surfactant monomer are known.

Determination of absolute molecular weight can be achieved through static light scattering techniques [12]. However, the preparation of samples for this technique can be time consuming. An estimate of molecular weight from DLS measurements can be determined using an empirical relationship between the hydrodynamic diameter and molecule/particle conformation. This molecular weight calculator has been incorporated into the Zetasizer Nano software.

A spherical particle, such as a triton X-100 micelle, with a hydrodynamic diameter of 7.5nm will give an estimated molecular weight of 72KDa. The average molecular weight of a triton X-100 monomer unit is 631Da [10]. Therefore, the aggregation

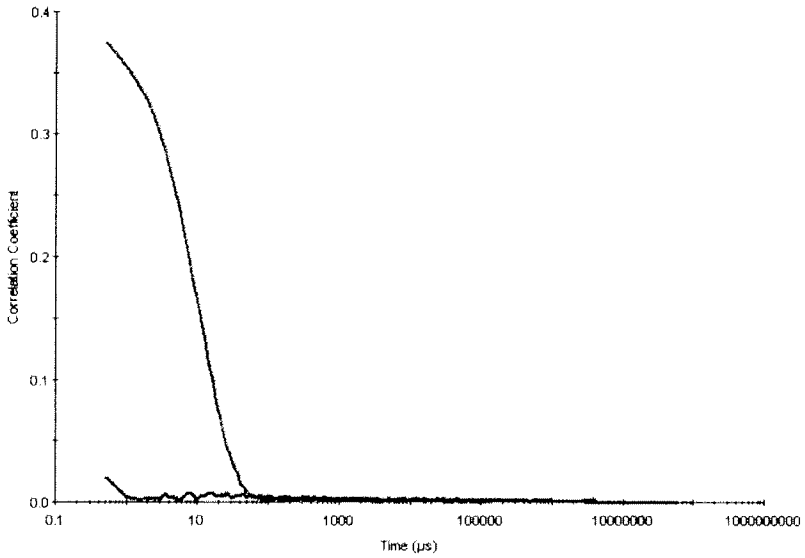


Figure 2: Correlation functions obtained for the 0.05mM (blue line) and 0.6mM (red line) concentrations of Triton X-100.

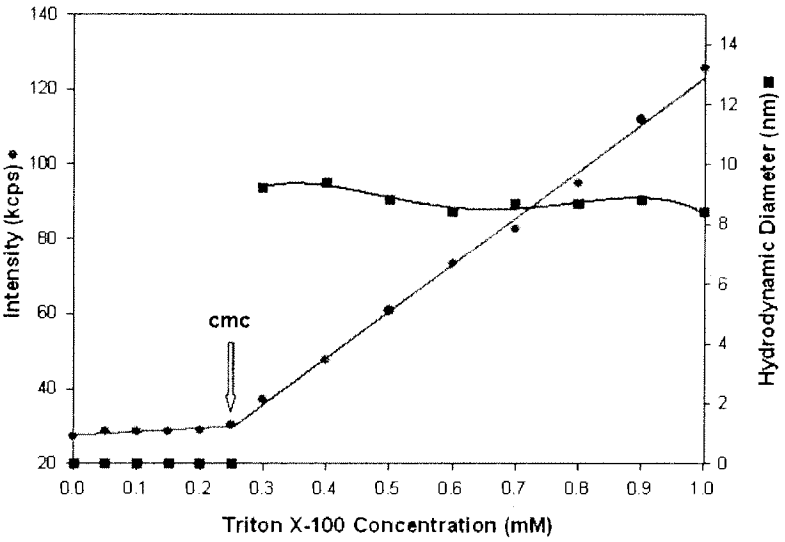


Figure 3: A plot of the intensity of scattered light (in kilo counts per second) and hydrodynamic diameter (in nanometres) obtained for various concentrations of triton X-100 prepared in deionised water. The intersection of the two lines at 0.25mM in the intensity data corresponds to the critical micelle concentration.

number of a triton X-100 micelle is 114. This corresponds with similar values reported in the literature obtained by other techniques [13, 14].

Studying the Effect of Surfactant Concentration on Micelle Size

Dynamic light scattering is an ideal technique for studying surfactant micelles as it is non-invasive and allows measurements to be made of the sample in its native environment.

The influence of surfactant concentration and dispersant conditions on the size and shape of surfactant micelles has been widely reported [15-17]. To illustrate the use of DLS in studying these effects, measurements were made on various concentrations of the ionic surfactant dodecyltrimethylammonium bromide (DTAB) in the presence of 0.1M sodium bromide. Figure 4 shows the z-average diameters (in nanometres) measured for a series of DTAB concentrations (in mM) prepared in 0.1M NaBr. There is a gradual decrease in the measured size as the surfactant concentration is increased. It can be seen from the sizes obtained, that the DLS technique is capable of monitoring changes of less than 1 nanometre.

It has been reported that this decrease in micelle size with increasing surfactant concentration results from high charge repulsion forces between the DTAB micelles which increase the diffusion speed of the micelles[15]. This corresponds to a decrease in the hydrodynamic diameter.

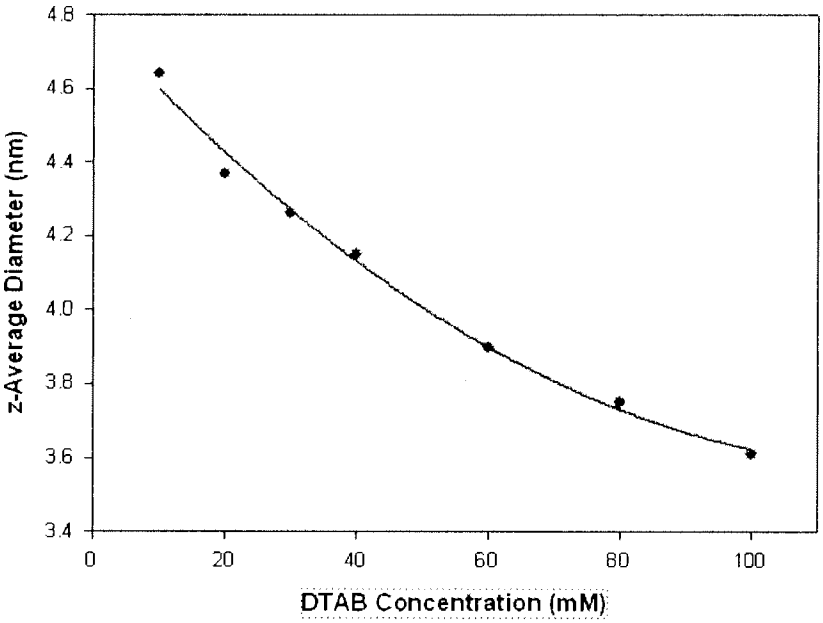


Figure 4: The z-average diameters (in nanometers) obtained for various concentrations of DTAB (in mM) prepared in 0.1M NaBr.

Conclusions

Dynamic light scattering is an ideal technique for the characterization of surfactant micelles. The results reported here illustrate the application of DLS in the study of various aspects of micelle characterization.

References

[1] D.H. Everett, Basic Principles of Colloid Science (1988) The Royal Society of Chemistry, Cambridge, UK.

[2] Colloid Science: Principles, Methods and Applications [Ed. T. Cosgrove] (2005) Blackwell, Oxford, UK.

[3] K.S. Birdi, Handbook of Surface and Colloid Chemistry (1997), CRC Press, Boca Raton, FL.

[4] A. Dominguez, A. Fernandez, N. Gonzalez, E. Iglesias, and L. Montenegro (1997) *J. Chem. Educ. 74,* 1227.

[5] Y. Nakahara, T. Kida, Y. Nakatsuji and M. Akashi (2005) *Langmuir 21,* 6688.

[6] German patent 19725211

[7] US patent 6016195

[8] Japan patent 2911877

[9] International Standard ISO13321 Methods for Determination of Particle Size Distribution Part 8: Photon Correlation Spectroscopy, International Organisation for Standardisation (ISO) 1996.

[10] Handbook of Industrial Surfactants [Compiled by M. Ash and I. Ash] (1993), Gower, UK.

[11] G.D.J. Phillies and J.E. Yambert (1996) *Langmuir 12,* 3431.

[12] K. Mattison and M. Kaszuba (2003) American Biotech. Lab. June

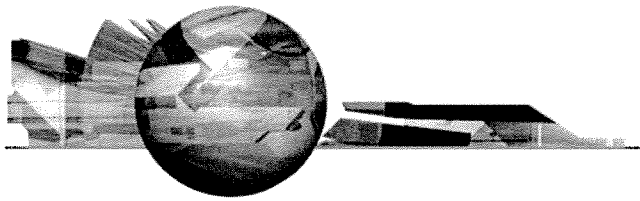
[13] C.J. Biaselle and D.B. Millar (1975) *Biophys. Chem. 3,* 355.

[14] P.J. Tummino and A. Gafni (1993) *Biophys. J. 64,* 1580.

[15] M. Pisarcik, F. Devinsky and E. Svajdlenka (1996) *Colloids and Surfaces 119,* 115.

[16] S. Ozeki and S. Ikeda (1982) J. *Colloid. Int. Sci. 87,* 424.

[17] V.K. Aswal and P.S. Goyal (2000) *Physical Review 61,* 2947.



Zetasizer Nano

The Zetasizer Nano system from Malvern Instruments is the first commercial instrument to include the hardware and software for combined static, dynamic, and electrophoretic light scattering measurements. The wide range of sample properties available for measurement with the Nano system include, particle size, molecular weight, and zeta potential.

The Zetasizer Nano system was specifically designed to meet the low concentration and sample volume requirements typically associated with pharmaceutical and biomolecular applications, along with the high concentration requirements for colloidal applications. Satisfying this unique mix of requirements was accomplished using a backscatter optical system and a novel cell chamber design. As a consequence of these features, the Zetasizer Nano specifications for sample size and concentration exceed those for any other commercially available dynamic light scattering instrument, with a size range of 0.6nm to 6um, and a concentration range of 0.1ppm to 40% w/v.

Complementing the patented hardware design is the Malvern software, providing instrument control and data analysis for the Zetasizer Nano System. The software uses self optimizing algorithms to automate the optical set-up required for each individual sample type, and includes a unique "one click" measure, analyze, and report feature designed to minimize the new user learning curve.

Malvern Instruments Ltd

Enigma Business Park · Grovewood Road · Malvern · Worcestershire · UK · WR14 1XZ
Tel: +44 (0)1684 892456 · Fax: +44 (0)1684 892789

Malvern Instruments Worldwide

Sales and service centers in over 50 countries for details visit www.malvern.com/contact

more information at www.malvern.com